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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,295	08/04/2006	Michel Chartrain	21502P	8419

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EXAMINER	
JOIKE, MICHELE K	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,295	CHARTRAIN ET AL.	
	Examiner	Art Unit	
	MICHELE K. JOIKE	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9-29,31 and 35-39* is/are pending in the application.

4a) Of the above claim(s) *21-29 and 39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,10-20 and 35-38* is/are rejected.

7)☒ Claim(s) *6 and 9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/4/06, 10/17/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on March 5, 2009 is acknowledged. The traversal is on the ground(s) that Chen et al do not teach prior selection of a highly productive clonal subtype shown to exhibit a higher plasmid copy number per cell when compared to other clonal subtypes. Therefore, Chen et al do not anticipate and a special technical feature can be found. This is not found persuasive because prior selection is not required by the claims, therefore, Chen et al do anticipate claim 1.

The requirement is still deemed proper and is therefore made FINAL.

Claims 21-29, 31 and 39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on March 5, 2009.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10, 14-20 and 37-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 10, the E. coli strain is cultivated on an industrial scale. It is unclear how much of to strain needs to be produced to be considered an industrial scale.

In claims 14 and 18, a solution is fed continuously to the culture when the clonal subtypes are in mid-logarithmic growth. However, it is a fed batch fermentation process, which usually means that concentrated amounts of nutrients are added, often at the start of fermentation. Therefore, it is unclear what is added initially to start growth of the clonal subtypes. Are minimal amounts of nutrients used to initially grow the cultures until mid-log phase? In other words, is it a continuous or exponential fed batch fermentation, or a combination of the two?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al.

Chen et al (IDS reference A, especially pages 43 and 44) teach a fed-batch fermentation process for *E. coli* that produces a total yield of 10-fold the

plasmid DNA as compared to manual fed-batch fermentation with the same plasmid transformed into the same *E. coli* strain.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4, 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cress et al in view of Korz et al.

Cress et al (IDS ref., pp. 635, 636, 638 and 639) teach a method for producing plasmid by isolating chromosomal mutants of E. coli that maintain higher levels of an F' plasmid and cultivating them. The mutants were initially

detected by selecting for increased lactose fermentation. The reference teaches that a well-established approach to detecting mutants with altered plasmid replication is to examine the bacterial population for increased expression of plasmid-linked genes. The mutants had 2-7 times more plasmids than unselected strains. The cells were cultured at 30°C for 24-30 hrs. Although, the cells were grown for 30 hrs, and not 48 hrs, one of ordinary skill in the art would know that time can be optimized depending on the strain and medium used for growth.

> A. Optimization Within Prior Art Conditions or Through Routine Experimentation
>
> Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be *prima facie* obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

However, Cress et al do not teach fed batch fermentation for culturing the cells.

Korz et al (IDS ref., pp. 59-60) teach a fed batch process for high cell density cultivation of E. coli. Glycerol was the carbon source, and the medium also contained KH_2PO4, $(NH_4)_2HPO_4$ and $MgSO_4.7H_2O$.

Additionally, as evidenced by microbelibrary.org, E. coli cells grown on blood agar are phenotypically gray.

The ordinary skilled artisan, desiring to use fed batch fermentation, would have been motivated to combine the teachings of Cress et al teaching for producing plasmid by isolating chromosomal mutants of E. coli that maintain higher levels of an F' plasmid and cultivating them with the teachings of Korz et al teaching fed batch fermentation because Korz et al state that E. coli is an important host organism for recombinant protein, and to maximize the volumetric productivities of bacterial cultures it is important to grow E. coli to high cell concentrations, like in fed batch fermentation. It would have been obvious to one of ordinary skill in the art because Cress et al teaches that the method has been successful to isolate mutants that harbor plasmids at increased levels. Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cress et al and Korz et al as applied to claims 1, 2, 4, 5, 11 and 12 above, and further in view of Mason et al.

Cress et al teach all of the limitations as described above. However, they do not teach use of DH5.

Korz et al teach all of the limitations as described above. However, they do not teach use of DH5.

Mason et al (IDS ref.) teaches using DH5α cells and increasing copy number of plasmids.

The ordinary skilled artisan, desiring to use DH5, would have been motivated to combine the teachings of Cress et al teaching for producing plasmid by isolating chromosomal mutants of E. coli that maintain higher levels of an F' plasmid and cultivating them with the teachings of Korz et al teaching fed batch fermentation and Mason et al because Mason et al state that DH5α cells help avoid possible secondary metabolic stress imposed by amino acid auxotrophy. It would have been obvious to one of ordinary skill in the art because Mason et al teach that DH5α influences plasmid copy number and overall gene expression. Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claims 13, 35 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cress et al and Korz et al as applied to claims 1, 2, 4, 5, 11 and 12 above, and further in view of Zhang et al.

Cress et al teach all of the limitations as described above. However, they do not teach use of KH_2PO4, K_2HPO_4 and $(NH_4)_2SO_4$ and glycerol.

Korz et al teach all of the limitations as described above. They teach using KH_2PO4, $(NH_4)_2HPO_4$ and $MgSO_4.7H_2O$ and glycerol. However, they do not teach use of K_2HPO_4 and $(NH_4)_2SO_4$ in the medium.

Zhang et al (IDS ref., especially pp. 410, 414, 416) teach use of chemically defined media, and the importance of PO_4 and SO_4 as basic nutrients, specifically using K_2HPO_4 and $(NH_4)_2SO_4$.

The ordinary skilled artisan, desiring to use media with KH_2PO4, K_2HPO_4 and $(NH_4)_2SO_4$ and glycerol, would have been motivated to combine the teachings of Cress et al teaching for producing plasmid by isolating chromosomal mutants of E. coli that maintain higher levels of an F' plasmid and cultivating them with the teachings of Korz et al teaching fed batch fermentation with KH_2PO4, $(NH_4)_2HPO_4$ and $MgSO_4.7H_2O$ and glycerol media and Zhang et al because Zhang et al state that chemically defined media support a more reproducible fermentation performance. It would have been obvious to one of ordinary skill in the art because Zhang et al teach that PO_4 and SO_4 are basic requirements for maximum growth in defined medium. Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Allowable Subject Matter

Claims 6 and 9 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHELE K. JOIKE whose telephone number is (571)272-5915. The examiner can normally be reached on M-F, 10:00-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571)272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michele K. Joike/
Examiner, Art Unit 1636

Michele K. Joike
Examiner
Art Unit 1636